

**> THE PATIENT**

52-year-old man

**> SIGNS & SYMPTOMS**

- Intermittent fevers
- Recently received second dose of COVID-19 vaccine
- Tremors in all 4 extremities

**> THE CASE**

A 52-year-old man sought care at the emergency department for intermittent fevers that started within 6 days of receiving his second dose of the BNT162b2 mRNA COVID-19 vaccine (Pfizer/BioNTech). After an unremarkable work-up, he was discharged home. Six days later, he returned to the emergency department with a fever of 102 °F and new-onset, progressive tremors in all 4 of his extremities.

The patient had a history of rheumatoid arthritis, for which he was taking oral methotrexate 15 mg once weekly and golimumab 50 mg SQ once monthly, and atrial fibrillation. He'd also had mechanical aortic and mitral valves implanted and was taking warfarin (9 mg/d on weekdays, 6 mg/d on Saturday and Sunday). Aside from his fever, his vital signs were normal. He also had horizontal nystagmus (chronically present) and diffuse tremors/myoclonic movements throughout his upper and lower extremities. The tremors were present at rest and worsened with intention/activity, which affected the patient's ability to walk and perform activities of daily living.

He was admitted the next day to the family medicine service for further evaluation. Neurology and infectious disease consultations were requested, and a broad initial work-up was undertaken. Hyperreflexia was present in all of his extremities, but his neurologic examination was otherwise normal. Initial laboratory tests demonstrated leukocytosis and elevated liver transaminases. His international normalized ratio (INR) and prothrombin time (PT) also were elevated (> 8 [goal, 2.5-3.5 for mechanical heart valves] and > 90 seconds [normal range, 9.7-13.0 seconds], respectively), thus his warfarin was held and oral vitamin K was started (initial dose of 2.5 mg, which was increased to 5 mg when his INR did not decrease enough).

By Day 2, his INR and PT had normalized enough to reinstate his warfarin dosing. Results from the viral antibody and polymerase chain reaction testing indicated the presence of cytomegalovirus (CMV) infection with viremia; blood cultures for bacterial infection were negative. Brain magnetic resonance imaging was ordered and identified a small, acute left-side cerebellar stroke. Lumbar puncture also was ordered but deferred until his INR was below 1.5 (on Day 8), at which point it confirmed the absence of CMV or herpes simplex virus in his central nervous system.

**THE DIAGNOSIS**

The patient started oral valganciclovir 900 mg twice daily to ameliorate his tremors, but he did not tolerate it well, vomiting after dosing. He was switched to IV ganciclovir 5 mg/kg every 12 hours; however, his tremors were not improving, leading the team to suspect an etiology other than viral infection. A presumptive diagnosis of autoimmune movement disorder was made, and serum tests were ordered; the results were positive for antiphospholipid antibodies, including anticardiolipin and anti- $\beta_2$  glycoprotein-I antibodies. A final diagnosis of autoimmune antiphospholipid antibody syndrome (APS)-related movement disorder<sup>1</sup> with coagulopathy was reached, and the patient was started on methylprednisolone 1 g/d IV.

**■ We suspected the CMV viremia was reactivated** by the COVID-19 vaccine and caused the APS that led to the movement disorder, coagulopathy, and likely, the thrombotic

**Aaron Lear, MD, MSc, CAQ; Ahmed Itrat, MD; Katherine C. Sheridan, MD, FAAFP**

Departments of Family Medicine (Drs. Lear and Sheridan) and Neurology (Dr. Itrat), Cleveland Clinic Akron General, Akron, OH

[Leara@ccf.org](mailto:Leara@ccf.org)

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➤ Limited evidence suggests that COVID-19 vaccination can cause reactivation of dormant herpesviruses.

cerebellar stroke. The case was reported to the Vaccine Adverse Event Reporting System (VAERS).<sup>2</sup>

## DISCUSSION

Clinically evident APS is rare, with an estimated annual incidence of 2.1 per 100,000 according to a 2019 longitudinal cohort study.<sup>3</sup> Notably, all identified cases in this cohort had either a venous or arterial thrombotic event—a characterizing feature of APS—with 45% of patients diagnosed with stroke or transient ischemic attack.<sup>3,4</sup>

The development of antiphospholipid antibodies has been independently associated with rheumatoid arthritis,<sup>5</sup> COVID-19,<sup>6</sup> and CMV infection,<sup>7</sup> as well as with vaccination for influenza and tetanus.<sup>8</sup> There also are reports of antiphospholipid antibodies occurring in patients who have received adenovirus-vectored and mRNA COVID-19 vaccines.<sup>9-11</sup>

■ **Movement disorders occurring with APS are unusual**, with approximately 1.3% to 4.5% of patients with APS demonstrating this manifestation.<sup>12</sup> One of multiple autoimmune-related movement disorders, APS-related movement disorder is most commonly associated with systemic lupus erythematosus (SLE), although it can occur outside an SLE diagnosis.<sup>4</sup>

While APS-related movement disorder occurs with the presence of antiphospholipid antibodies, the pathogenesis of the movement disorder is unclear.<sup>4</sup> Patients are typically young women, and the associated movements are choreiform. The condition often occurs with coagulopathy and arterial thrombosis.<sup>4</sup> Psychiatric manifestations also can occur, including changes in behavior—up to and including psychosis.<sup>4</sup>

■ **Evidence of COVID-19 vaccination reactivating herpesviruses exists**, although it is rare and usually does not cause serious health outcomes.<sup>13</sup> The annual incidence of reactivation related to vaccination is estimated to be 0.7 per 100,000 for varicella zoster virus and 0.03 per 100,000 for herpes simplex virus.<sup>13</sup> The literature also suggests that the occurrence of Bell palsy—the onset of which may be related to the reactivation of a latent

virus—may increase in relation to particular COVID-19 vaccines.<sup>14,15</sup> Although there is no confirmed explanation for these reactivation events at this time, different theories related to altering the focus of immune cells from latent disease to the newly generated antigen have been suggested.<sup>16</sup>

To date, reactivation has not been demonstrated with CMV specifically. However, based on the literature reviewed here on the reactivation of herpesviruses and the temporal relationship to infection in our patient, we propose that the BNT162b2 mRNA vaccination reactivated his CMV infection and led to his APS-related movement disorder.

■ **Treatment is focused on resolving the autoimmune condition**, usually with corticosteroids. Longer-term treatment of the movement disorder with antiepileptics such as carbamazepine and valproic acid may be necessary.<sup>4</sup>

■ **Our patient received** methylprednisolone IV 1 g/d for 3 days and responded quickly to the treatment. He was discharged to a post-acute rehabilitation hospital on Day 16 with a plan for 21 days of antiviral treatment for an acute CMV infection, 1 month of oral steroid taper for the APS, and continued warfarin treatment. This regimen resulted in complete resolution of his movement disorder and negative testing of antiphospholipid antibodies 16 days after he was discharged from the hospital.

## THE TAKEAWAY

This case illustrates the possible reactivation of a herpesvirus (CMV) related to COVID-19 vaccination, as well as the development of APS-related movement disorder and coagulopathy related to acute CMV infection with viremia. Vaccination for the COVID-19 virus is seen as the best intervention available for preventing serious illness and death associated with COVID-19 infection. Thus, it is important to be aware of these unusual events when vaccinating large populations. This case also demonstrates the need to understand the interplay of immune status and possible disorders associated with autoimmune conditions. Keeping an open mind when evaluating patients with post-vaccination complaints

is beneficial—especially given the volume of distrust and misinformation associated with COVID-19 vaccination. **JFP**

#### CORRESPONDENCE

Aaron Lear, MD, MSc, CAQ, Cleveland Clinic Akron General Center for Family Medicine, 1 Akron General Avenue, Building 301, Akron, OH 44307; Leara@ccf.org

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## PRACTICE ALERT

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systematic review of 31 studies (mostly low-quality observational studies and case series) conducted by the ACIP Influenza Work Group found no risk for severe anaphylaxis, hospitalization, or death, even in those with a history of an anaphylactic reaction to eggs.<sup>2</sup> A review of Vaccine Adverse Events Reporting System (VAERS) data identified 18 cases of reported anaphylaxis after receipt of an inactivated influenza vaccine over a 5-year period, but clinical review confirmed only 7.<sup>2</sup>

And finally, appropriate precautions already are recommended for administration of any vaccine. The CDC guidance for best practices for administering vaccines states: "Although allergic reactions are a common concern for vaccine providers, these reactions are uncommon and anaphylaxis following vaccines is rare, occurring at a rate of approximately one per million doses for many vaccines. Epinephrine and equipment for managing an airway should be available for immediate use."<sup>4</sup>

#### ■ What does this mean in practice?

Family physicians who administer influenza vaccines do not need to use special precautions for any influenza vaccine, or use non-

egg-based vaccines, for those who have a history of egg allergy. However, they should be prepared to respond to a severe allergic reaction just as they would for any other vaccine. Any vestigial practices pertaining to egg allergy and influenza vaccines—such as vaccine skin testing prior to vaccination (with dilution of vaccine if positive), vaccination deferral or administration via alternative dosing protocols, and split dosing of vaccine—are unnecessary and should be abandoned. **JFP**

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